DETAILED ACTION

The amendment filed 11/09/2007 has been entered. Claims 1 and 3–15 are pending and being examined.

Maintained formal matters, objections, and/or rejections:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3–7 and 12–15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Makishima (WO 96/33215) in view of Makishima (U. S. Patent No. 7,235,527), Ron (U. S. Patent No. 5,171,579) and Avis (1990).

The teachings of Makishima (WO 96/33215) in view of Makishima (U. S. Patent No. 7,235,527) are of record in the last Office action at page 2, line 8 through page 3, line 6. The teachings of Makishima (WO 96/33215) in view of Makishima (U. S. Patent No. 7,235,527), Ron and Avis are of record in the last Office action, page 3, line 7 through page 6, line 20.

In addition, Avis teaches that after a product has been compounded, it must be filtered if it is a solution. The primary objective of filtration is to clarify a solution. A high degree of clarification is termed "polishing" a solution. This term is used when particulate matter down to approximately 2 μm in size is removed. A further step, removing particulate matter down to 0.2

μm in size, would eliminate microorganisms and would accomplish "cold" sterilization. A high degree of clarity conveys the impression of high quality and purity, desirable characteristics for a parenteral solution. (Avis, page 1561, left column, full paragraph 1).

During the filling of containers with a product, the most stringent requirements must be exercised to prevent contamination, particularly if the product has been sterilized by filtration and will not be sterilized in the final container. Under the latter conditions the process is usually called an "aseptic fill." (Avis, page 1561, paragraph bridging left and right columns).

Many products, both pharmaceutical and biological, will be affected adversely by the elevated temperatures required for thermal sterilization. Such products must, therefore, be sterilized by a nonthermal method. Most thermolabile solutions may be sterilized by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner. (Avis, page 1564, right column, full paragraph 1).

For most pharmaceuticals and biologicals the liquid product is sterilized by filtration and then filled into the dosage container aseptically (Avis, page 1566, left column, full paragraph 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to filter the solution of MP52 and mannitol prior to lyophilization with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification to clarify the solution, to eliminate microorganisms and accomplish "cold" sterilization, and to convey the impression of high quality and purity. It would have been further obvious to one of ordinary skill in the art at the time of Applicants' invention to fill a sterile vessel with the resulting filtered aqueous solution with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make such a modification because during the

filling of containers with a product, the most stringent requirements must be exercised to prevent contamination, particularly if the product has been sterilized by filtration and will not be sterilized in the final container, and a sterile vessel would help prevent contamination.

Therefore, Makishima (WO 96/33215) in view of Makishima (U. S. Patent No. 7,235,527), Ron and Avis teach a lyophilized composition of MP52, wherein said composition is made by mixing an aqueous solution of human MP52 and mannitol, filtering the resulting aqueous solution, filling a sterile vessel with the resulting filtered aqueous solution, and lyophilizing said filtered aqueous solution in said sterile vessel, wherein said human MP52 and mannitol are mixed at a weight ratio of 1:5-50.

The invention is prima facie obvious over the prior art.

Response to Arguments

Applicants argue that:

> The present claims indicate that the aqueous solution containing MP52 and mannitol is filtered prior to lyophilization. The addition of mannitol to the aqueous MP52 solution results in a higher concentration of MP52. The addition of mannitol has unexpectedly been found to produce an MP52 solution with good solubility and no aggregates. This allows the MP52 to be filtered without losing large amounts of MP52 due to the retention of aggregates by the filter. If lyophilization is carried out without mannitol or filtering, the aggregates would be lyophilized and maintained after redissolution. These aggregates could interfere with the administered dose and injection. The Avis reference provides a general discussion of lyophilization but has nothing to do with proteins in particular and thus does not suggest the use of mannitol and filtering to prevent aggregates of MP52. Ron does not cure the deficiencies in Avis as Ron does not suggest that mannitol is suitable for the use in a filtered and lyophilized product of MP52 either. Makishima (WO 96/33215) and U.S. Patent No. 7,235,527 do not cure the deficiencies in Ron and Avis as neither Makishima reference suggests or discloses the addition of mannitol combined with filtration to avoid aggregates. In addition, neither Makishima reference suggests or discloses a weight ratio of 1: 5-50. Since none of the cited references individually or in combination suggest the use of mannitol and filtration to produce a lyophilized composition without aggregates, applicants request that this rejection be withdrawn.

Applicants' arguments have been fully considered but they are not persuasive. Patentability requires novelty and unobviousness in light of the prior art, not in light of what the inventor knew and included in his patent application. Anticipation and obviousness are measured by what was previously known to persons in the field of the invention. There is no evidence of record regarding the expected effects of mannitol on MP52 solubility and aggregation. Therefore, these results cannot be called "unexpected." Furthermore, the prior art suggest doing exactly what applicants are claiming. Specifically, Makishima (WO 96/33215) teaches compositions comprising human MP52 that are prepared by adding one or more of suitable water-soluble excipients, such as mannitol, to human MP52, dissolving the mixture in water, dividing it into vials or ampoules followed by lyophilizing and hermetically sealing. Therefore, Makishima's composition and process of preparation necessarily possess the benefits of a higher concentration of MP52 in the filtered solution, good solubility and no aggregates. Even though these benefits are not recognized by Makishima, applicant's recognition of these benefits is not in itself sufficient to distinguish the claimed compositions or process of preparation from the prior art because prima facie obviousness is not rebutted by merely recognizing additional advantages or latent properties present in the prior art

Claims 8–11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Makishima (WO 96/33215) in view of Makishima (U. S. Patent No. 7,235,527), Ron (U. S. Patent No. 5,171,579) and Avis (1990) as applied to claim 7 above, and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-30).

Response to Arguments

Applicants argue that:

> Claims 7-14 were rejected under 35 USC §103(a) as unpatentable over Makishima (WO 96/33215) and U.S. Patent No. 7,235,527 in view of Ron and Avis further in view of Chang. Chang does not suggest the use of mannitol and filtration to prepare a lyophilized MP52 composition and thus Chang does not cure the deficiencies in Makishima (WO 96/33215) and U.S. Patent No. 7,235,527 in view of Ron and Avis. There is no suggestion in any of the cited art that mannitol can be used to prevent aggregates which allows the MP52 solution to be filtered prior to lyophilization. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants' arguments have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The examiner has already addressed the alleged deficiencies in Makishima (WO 96/33215), above.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Makishima (WO 96/33215) in view of Makishima (U. S. Patent No. 7,235,527), Ron (U. S. Patent No. 5,171,579) and Avis (1990) and further in view of Chang (J Pharm Sci. 1996 Dec;85(12):1325-30) as applied to claims 7–9 above, and further in view of Hansen (U. S. Patent No. 6,586,574) and in light of the MeSH definition of "poloxamer."

Response to Arguments

Applicants argue that:

> … the combination of Makishima (WO 96/33215) and U.S. Patent No. 7,235,527, Ron, Avis and Chang, does not suggest that mannitol should be used prior to filtration when lyophilizing MP52. Hansen is cited only for the disclosure of surfactants for stabilization of freeze-dried proteins and does not cure the deficiencies in Makishima (WO 96/33215) and U.S. Patent No. 7,235,527, Ron, Avis and Chang regarding the use of mannitol with MP52 in a filtered,

Applicants' arguments have been fully considered but they are not persuasive. As discussed above, Avis teaches that after a product has been compounded, it must be filtered if it is a solution. The primary objective of filtration is to clarify a solution. A further step, removing particulate matter down to 0.2 μm in size, would eliminate microorganisms and would accomplish "cold" sterilization. Therefore, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to filter the solution comprising MP52 and mannitol with a reasonable expectation of success. One of ordinary skill in the art would be motivated to mate this modification to clarify the solution and accomplish "cold" sterilization. The examiner believes he has answered all pertinent arguments. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

/DAVID ROMEO/
PRIMARY EXAMINER
ART UNIT 1647

DSR
January 25, 2008